

Intraperitoneal Chemotherapy in Ovarian Cancer Remains Experimental

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Intraperitoneal (IP) chemotherapy was not standard treatment for patients with optimally debulked ovarian cancer before January 4, 2006. A National Cancer Institute (NCI; Bethesda, MD) statement posted on the Internet¹ proclaims a change of practice, and it followed the publication by Armstrong et al and an accompanying editorial in the *New England Journal of Medicine*.^{2,3} The NCI press statement talks about “prejudice” against the old idea of IP chemotherapy but apparently there is “now firm data showing that we should use a combination of IP and intravenous (IV) chemotherapy in most women with advanced ovarian cancer who have had successful surgery to remove the bulk of their tumor.” The Chairman of the Gynecologic Oncology Group (GOG) states in the same NCI announcement that randomized multicenter trials, including that of Armstrong et al “clearly show the value of IP chemotherapy.”¹ The President of the Society of Gynecologic Oncology says that she now knows that “the longest survival may be achieved by giving chemotherapy directly into the abdomen.”¹ Finally, the Chairman of the Board of the Gynaecologic Cancer Foundation is quoted as looking forward to working with the NCI and the ovarian cancer community “to educate women about the results of this very important clinical trial.”¹ Well, let three European oncologists help in this education process.

There are at least eight reasons why the Armstrong article does not support the use of IP administration as a standard of care.

The publication by Armstrong et al has a *P* value of .03 for comparing overall survival that although reaches statistical significance, only just meets this criteria. In fact, the upper limit of the reported confidence interval reaches 0.97. However, this analysis was not based on a true intention-to-treat analysis; 14 randomly assigned patients were not included in the survival calculation, with nearly twice as many of those patients assigned to intraperitoneal treatment being excluded (five v nine patients). These numbers are, of course, small in comparison to the total number of women randomly assigned but the statistical significance is so small in this study, with the upper limit of the confidence interval reaching 0.97, that such minor imbalances could take the confidence limits over unity and render the trial statistically nonsignificant. The authors of the article, as well as those quoted on the NCI statement,¹ must clarify whether a true intention-to-treat analysis shows statistical significance in this trial or not.

Furthermore, more patients in the experimental arm (IP chemotherapy) were lost to follow-up, compared with those treated in the control arm (11 v five patients). Such differences are not usually a concern. However, there were 127 and 101 patient deaths in the control and IP arms of the trial, respectively, and as few as three additional patient deaths in the IP arm could make the result nonsignificant. The statistical difference between the two arms of the trial is so marginal that these differences in eligibility or loss of follow-up need to be investigated further.

The absolute difference in patients alive (15 patients) was less than those patients lost to follow-up (16 patients; 11 in the IP arm), and this is a very small proportion of the total population. It must be questioned whether such toxic treatment should be introduced as standard, based on such small differences and patient numbers.

In addition, the difference with respect to progression-free survival (PFS) was even smaller (nine more patients alive without recurrence in the IP arm), and comparisons for PFS failed significance (*P* = .05). Taking into account that in the end all patients with relapsed ovarian cancer will die, the difference with respect to survival will decrease further over time, and possibly fairly quickly, given the statistical marginality of the overall survival benefit.

The main difference between the two arms of the trial occurred after progression or relapse. Differences in median PFS between control patients and those treated with IP therapy were 2.4 and 2.9 months for those with microscopic and macroscopic residual disease, respectively; neither of these differences were statistically significant. In contrast, the differences in median overall survival were 12.5 months in patients with gross residual disease and 15.9 months in the whole population. There are only two possible explanations for this observation. Either patients who relapse after IP therapy live longer because the nature of the treatment has altered the biology of their disease, or patients who relapse after IP therapy are able to receive more effective second-line treatment. This finding of a relatively larger impact on overall survival than progression-free survival is not unique, in fact, it was seen in the original studies that defined the role of paclitaxel in first-line regimens (GOG111 and OV10).

There are at least three randomized phase III trials (International Collaborators in Ovarian Neoplasm [ICON4]/Arbeitsgemeinschaft Gynaekologische Onkologie Study Group Ovarian Cancer [AGO-OVAR2.2]),⁴ Gore et al,⁵ and Gordon et al⁶) that are

supported by two smaller trials,^{7,8} that show a significant impact of second-line therapy on overall survival in relapsed ovarian cancer. However, in the case of ICON 4/AGO-OVAR 2.2, some have argued that the improved overall survival rates could have been because a majority of patients had not received a taxane during first-line therapy, although subgroup analysis failed to show this to be the case. These results prompted the Gynecologic Cancer Intergroup (GCIg) Third International Consensus Conference on Ovarian Cancer 2005 to select progression-free survival as the preferable primary end point in first-line therapy trials.^{9,10} Unfortunately, Armstrong et al did not report any details on how patients were treated at relapse.² Therefore, it remains a possibility that any overall survival benefit observed for patients treated with IP therapy is an epiphenomenon and is related to differences in second-line treatment.

This patient population of the Armstrong study is similar to those patients treated by the GOG in their study (protocol 158) as reported by Ozols et al,¹¹ and to the optimally debulked (stratum 1) patients treated in the AGO-OVAR trials reported by du Bois et al^{12,13} and Pfisterer et al.¹⁴ These four trials showed median overall survival in optimally debulked patients of 57.4, 59.5, 57.0, and 56.5 months, respectively, for those patients treated with IV carboplatin/paclitaxel. The Armstrong study did rather poorly in comparison (median survival, 49.7 months). Cross trial comparisons lack the validity of those generated by prospective randomization. However, the marginal statistical differences in the Armstrong trial should be interpreted cautiously in the light of the results from of the studies involving IV carboplatin/paclitaxel.

One of the main problems with intraperitoneal therapy is its toxicity. The Armstrong trial merely confirms this, even when given in the context of a well-run trial whose authors are experts in the field. The article rightly points out that 42% of patients received six cycles of designated intraperitoneal therapy, that is to say that nearly 60% of patients didn't. Closer examination of the data reveals an even more startling finding: it appears that 8% of patients failed to receive any IP therapy and 34% of patients received only one or two cycles. Can two cycles of chemotherapy in a third of the study's patients really contribute to this result, or is the effect of six cycles of IP therapy in a minority of patients so large as to make this trial positive? The effect of only a relatively small number of cycles of IP therapy in this trial is out of proportion to the level of benefit seen in the only positive study of intraperitoneal chemotherapy, which was published in the early 1990s by Alberts et al.¹⁵

Patients assigned to the IP arm not only received far less IP cisplatin/paclitaxel than planned but also substantial amounts of off-study therapy (ie, 84 of 170 patients receiving six courses of therapy had IV therapy and 44% of them received carboplatin/paclitaxel). This makes any definitive conclusion about the experimental arm even more difficult. The administration of far less toxic therapy (IV carboplatin/paclitaxel) may allow more subsequent lines of treatment to be delivered and this could have had an influence on the result. The variety of regimens and schedules actually used in the experimental arm of the Armstrong study makes it impossible to recommend any specific treatment based on the results of this patient group. All one can say for sure is that one cannot recommend six cycles of an IP regimen that is undeliverable to the majority of women.

The striking difference in the level of toxicity between the intravenous and intraperitoneal groups is shown by the compara-

tive frequency of grade 3/4 adverse events and by quality of life comparisons up to 6 weeks after the final cycle of treatment. These differences are impressive. However, if one then examines the considerable and significant differences in toxicity and quality of life between the control arm of this study (cisplatin/paclitaxel) and the standard of care (carboplatin plus paclitaxel), then the IP regimen as described by Armstrong et al is even more toxic than it appears. It is also of note that the IP regimen described here is not only more toxic than the control arm regimen or the current standard treatment, but is also worse in this regard than the previously used schedules in the two trials that the NCI holds up as supportive evidence for the efficacy of IP therapy in general. In those studies, 58% to 71% of patients were able to tolerate six cycles of IP treatment, substantially more than the 42% in the Armstrong trial.

The trial design is poor because it confuses two questions. First, there is the question of whether an IP regimen (any IP regimen) is better than the "standard of care." Such a trial is important to perform and would require the control arm to be the standard of care, ie, IV carboplatin plus paclitaxel. This is not the case in this trial because the control arm is not standard of care, it is IV cisplatin plus paclitaxel given over a period of 24 hours. The authors might argue that the trial is designed to examine whether or not IP administration of one or two drugs is better than IV administration. The trial design even fails to address this question because the doses and schedules of the two drugs, namely cisplatin and paclitaxel, are different in the two arms of the study. Therefore, it is impossible to dissect out the variation in treatment that is responsible for any benefit, in other words, is it really the route of administration or is it the dose-density of the paclitaxel schedule. The latter factor has already been shown to be of significance in terms of efficacy in other tumor types such as breast cancer.¹⁶

Unfortunately, the Armstrong study continues a long tradition of IP trials with confusing designs. The NCI announcement summarizes six other first-line trials in advanced ovarian cancer that evaluate the role of IP as opposed to IV therapy. Only two of these six trials ever used similar regimens for the control and experimental groups. Furthermore, the IP experimental arms of the trials have differed in every study. Some trials included both IV and IP therapy in the experimental arm, others have added additional drugs into one arm only, and in only three trials have equivalent platinum doses been compared.

Furthermore, the majority of these six trials were underpowered with fewer than 200 patients enrolled. Accordingly, the results of all these trials shed little light on the controversy of IP therapy: four trials were completely negative,¹⁷⁻²⁰ one trial was negative and was only rendered statistically significant after expanding recruitment beyond the originally planned patient numbers,¹⁵ and one trial was only positive according to a one-tailed test of progression-free survival but negative with respect to overall survival.²¹ Interestingly, the authors of the last study concluded that "the experimental (IP) arm is not recommended for routine use."

It is surprising how anyone can use these previous trials with all their limitations to support the conclusions of the Armstrong trial, which begs more questions than it answers. Armstrong and her colleagues need to provide an intention-to-treat analysis and provide evidence that second-line treatment did not differ substantially between the two arms of their trial. The only legitimate conclusion the authors of the NCI statement can then make, assuming the result is

still marginally statistically significant, is that this particular and hugely toxic regimen is better than an obsolete control arm. A control arm, which, incidentally, has proven higher toxicity rates and inferior quality of life compared with the actual standard of care (IV carboplatin/paclitaxel) in advanced ovarian cancer.

Armstrong et al are dedicated and valued colleagues of the highest ability and integrity. Their study is an important contribution to the literature and the candor with which they have presented their results, particularly the complication rates, is to be applauded. IP therapy may well have a role in the future management of women with ovarian cancer and indeed most study groups would probably be willing to participate in studies to define its role. However, at the present time, we have no IP regimen to offer women that is both safe and has a level 1 evidence-base for efficacy compared with the standard of care, namely carboplatin/paclitaxel delivered intravenously.

Women should not be subjected to intraperitoneal chemotherapy outside the context of properly designed clinical trials. These trials must either assess IP therapy in comparison to standard treatment or address the issue of route of administration for equivalent doses and schedules of the same drugs, not a mosaic of these questions.

In the meantime, can someone come up with a sensible IP regimen?

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